DOCUMENT RESUME

ED 122 467 EC 082 842

TITLE First Report of the Preliminary Findings and Recommendations of the Interagency Collaborative Group on Hyperkinesis.
INSTITUTION Interagency Collaborative Group on Hyperkinesis, Washington, D.C.
PUB DATE 76
NOTE 94p.

EDRS PRICE MF-$0.83 HC-$4.67 Plus Postage.
DESCRIPTORS *Behavior Problems; *Drug Therapy; Emotionally Disturbed; Etiology; Exceptional Child Research; *Hyperactivity; Incidence; Models; *Nutrition; Research Design; Research Reviews (Publications); Therapy

ABSTRACT

Presented is the preliminary report of the Interagency Collaborative Group on Hyperkinesis (ICGH) with functions which include exchanging information, coordinating expertise, evaluating existing data from ongoing research and reviewing proposed research for the purpose of making recommendations concerning hyperkinesis and dietary factors. The report contains sections on the definition of the hyperkinetic syndrome; diagnosis of hyperkinetic disorders; prevalence of the syndrome; factors (social, biochemical, nutritional, and allergy or intolerance to substances) related to hyperkinetic disorders; toxic reactions; safety testing of food additives; treatment programs; dietary intervention; research relevant to B. Feingold's hypothesis; minimum design requirements for a dietary study; and model research designs. Included among the recommendations of ICGH is that a valid assessment of the Feingold dietary regimen be designed to test the general therapeutic change that may follow from a mixture of the regimen's components. Appended is a report on the use of stimulant drugs in the treatment of behaviorally disturbed young school children which covers such issues as the promotion of drugs by industry and the media, the risk of drug dependency in later years, and the rights of parents. (SB)

****
* Documents acquired by ERIC include many informal unpublished *
* materials not available from other sources. ERIC makes every effort *
* to obtain the best copy available. Nevertheless, items of marginal *
* reproducibility are often encountered and this affects the quality *
* of the microfiche and hardcopy reproductions ERIC makes available *
* via the ERIC Document Reproduction Service (EDRS). EDRS is not *
* responsible for the quality of the original document. Reproductions *
* supplied by EDRS are the best that can be made from the original. *
****

ED122467

EC

U S DEPARTMENT OF HEALTH,
EDUCATION & WELFARE
NATIONAL INSTITUTE OF
EDUCATION

THIS DOCUMENT HAS BEEN REPRODUCED EXACTLY AS RECEIVED FROM THE PERSON OR ORGANIZATION ORIGINATING IT. POINTS OF VIEW OR OPINIONS STATED DO NOT NECESSARILY REPRESENT OFFICIAL NATIONAL INSTITUTE OF EDUCATION POSITION OR POLICY

FIRST REPORT OF THE

PRELIMINARY FINDINGS AND RECOMMENDATIONS

OF

The Interagency Collaborative Group on Hyperkinesis

Submitted to

The Assistant Secretary for Health

U.S. Department of Health, Education and Welfare

ED082842

CONTENTS

Members, Interagency Collaborative Group on Hyperkinesis..... ii

INTRODUCTION..... 1

DEFINITIONS..... 4

DIAGNOSIS OF HYPERKINETIC DISORDERS..... 5

PREVALENCE..... 6

FACTORS RELATED TO HYPERKINETIC DISORDERS..... 9

A. Social Factors.....10

B. Biochemical Factors.....12

C. Nutritional Factors.....13

D. Allergy or Intolerance to Substances.....21

TOXIC REACTIONS.....25

SAFETY TESTING OF FOOD ADDITIVES.....27

TREATMENT PROGRAMS.....33

DIETARY INTERVENTION.....36

REVIEW OF COMPLETED RESEARCH RELEVANT TO THE FEINGOLD HYPOTHESIS.....41

MINIMUM DESIGN REQUIREMENTS FOR A DIETARY STUDY.....47

MODEL DESIGNS.....55

Model Design A.....55

Model Design B.....57

Model Design C.....58

Model B and C Combined.....62

SUMMARY.....62

RECOMMENDATIONS.....66

INTERAGENCY COLLABORATIVE GROUP ON HYPERKINESIS

Chairman

Albert C. Kolbye, Jr., M.D.
Associate Director for Sciences
Bureau of Foods, Food and Drug Administration

Members

David Boesel, Ph.D.
Head, School Discipline Studies Staff
National Institute of Education

Charlotte Catz, M.D.
Perinatal and Infant Mortality Program
National Institute for Child Health
and Human Development

Joginder G. Chopra, M.D.
Special Assistant for Medical Affairs
Office of the Associate Director for
Nutrition and Consumer Sciences
Bureau of Foods, Food and Drug Administration

Jay J. Cinque
Division of Neuropharmacological Drug Products
Bureau of Drugs, Food and Drug Administration

Gerald F. Combs, Ph.D.
Nutrition Program Director
National Institute of Arthritis, Metabolism
and Digestive Diseases

Frank Cordle, Ph.D., M.P.H.
Epidemiologist in Charge, Epidemiology Unit
Office of the Associate Director for Sciences
Bureau of Foods, Food and Drug Administration

Allan Forbes, M.D.
Acting Associate Director for Nutrition and
Consumer Sciences
Bureau of Foods, Food and Drug Administration

Hyman Gittes
Division of Toxicology
Office of the Associate Director for Sciences
Bureau of Foods, Food and Drug Administration

Members (Continued)

Stephen P. Hersh, M.D.
Chief, Center for Studies of Child and Family
Mental Health
National Institute of Mental Health

James G. Hill
Assistant to the Director
National Institute of Child Health and Human
Development

Ronald S. Lipman, Ph.D.
Psychopharmacology Research Branch
National Institute of Mental Health

Kathryn R. Mahaffey, Ph.D.
Assistant to the Director
Division of Nutrition
Office of the Associate Director for Nutrition and
Consumer Sciences
Bureau of Foods, Food and Drug Administration

Mary Lee Metscher
Consumer Safety Officer
Office of the Associate Director for Compliance
Bureau of Foods, Food and Drug Administration

Karen Nelson, M.D.
Development Neurology Branch
National Institute of Neurological and Communicative
Disorders and Stroke

Geraldine Norris
Deputy Associate for Training and Research
Office of Maternal and Child Health
Bureau of Community Health Services

Andrew Porter, Ph.D.
Chief, Measurement and Methodology Division
National Institute of Education

Ellen Silbergeld, Ph.D.
Staff Fellow, Laboratory Neuropharmacology
National Institute of Neurological and Communicative
Disorders and Stroke

Paul C. Rambaut, Ph.D.
Assistant to the Acting Associate Director for Nutrition
and Consumer Sciences
Bureau of Foods, Food and Drug Administration

Members (Continued)

Merrill S. Read, Ph.D.
Acting Deputy Director, Center for Research for
Mothers and Child
National Institute for Child Health and Human Development

Natalie Reatig
Psychopharmacology Research Branch
National Institute of Mental Health

Barry Rosloff, Ph.D.
Division of Neuropharmacological Drug Products
Bureau of Drugs, Food and Drug Administration

Joy G. Schulterbrandt
Deputy Chief, Center for Studies of Child and Family
Mental Health
National Institute of Mental Health

Howard N. Seltzer
Deputy Director for Program Development and
Implementation
Office of Consumer Affairs
Office of the Secretary
Department of Health, Education and Welfare

Thomas J. Sobotka, Ph.D.
Biochemical Toxicology Branch
Office of the Associate Director for Sciences
Bureau of Foods, Food and Drug Administration

Janet A. Springer
Division of Mathematics
Office of the Associate Director for Sciences
Bureau of Foods, Food and Drug Administration

David Symmes, M.D.
Head, Section on Brain and Behavior
National Institute for Child Health and Human
Development

John E. Vanderveen, Ph.D.
Acting Director, Division of Nutrition
Office of the Associate Director for Nutrition
and Consumer Sciences

James S. Winbush, Jr.
Supervisory Mathematical Statistician
Division of Mathematics
Office of the Associate Director for Sciences
Bureau of Foods, Food and Drug Administration

INTRODUCTION

The Interagency Collaborative Group on Hyperkinesis (ICGH) held its first organizational meeting on July 31, 1975 at the Parklawn Building. In attendance at the meeting were representatives from the Bureaus of Food and Drugs, Food and Drug Administration, National Institute of Education, National Institute of Mental Health, National Institute for Child Health and Human Development, National Institute of Neurological, Communicative Disorders and Stroke, and the Bureau of Community Health Services.

As a result of the exchange of information between the scientists on the Interagency Group, the Assistant Secretary for Health set forth the functions which the ICGH should perform. These are:

a. Exchange information, coordinate expertise, evaluate existing data from ongoing research and review proposed research for the purpose of making findings and recommendations to the Assistant Secretary for Health concerning hyperkinesis and dietary factors.

   1. The findings shall speak to the significance of available data, the relevant issues, parameters studied and criteria employed, in order to resolve whether or not dietary modifications contribute significantly to a reduction of symptoms in hyperkinetic children.

2. Recommendations shall include the description of needed research, the parameters to be studied, the recommended experimental design, the suggested priority of effort, and funding mechanism to be employed.

b. The ICGH shall, from time to time, seek the advice and guidance of recognized investigators in the area of hyperkinesis.

c. The ICGH shall report its preliminary findings and recommendations to the Assistant Secretary for Health by October 31, and shall meet, when deemed appropriate by its chairman, to fulfill its mission of expediting the resolution of the relevant issues.

d. The ICGH should consider the means by which suitable research proposals should be solicited and funded. The group should function to expedite, but not circumvent, existing review and funding mechanism.

At subsequent meetings, subcommittees were organized to research and discuss these various functions.

On September 30, 1975, a conference was held to discuss research in hyperkinesis (see Appendix for Report) with invited speakers from several universities. These speakers included:

Keith Conners, Ph.D.
Department of Psychiatry, School of Medicine
University of Pittsburgh

Esther Wender, M.D.
Department of Pediatrics, College of Medicine
University of Utah

George Kerr, M.D.
Department of Nutrition, School of Public Health
Harvard University

J. P. Harley, Ph.D.
Department of Neurology
University of Wisconsin

Richard J. Schain, M.D.
Division of Pediatric Neurology
University of California - Los Angeles

Ben Feingold, M.D.
Department of Allergy
Kaiser Permanente Medical Center

Sheldon Margan, M.D.
Department of Nutritional Sciences
University of California - Berkeley

Bernard Weiss, Ph.D.
Department of Radiation Biology and Physics
University of Rochester

Morris Lipton, M.D.
Department of Psychiatry, School of Medicine
University of North Carolina

Additional meetings of the ICGH on October 15, 22 and 31 were concerned with the preparation of the preliminary findings and recommendations to be presented to the Assistant Secretary for Health. It is anticipated that the ICGH shall continue to meet in order to complete the preparation of detailed protocols for carrying out the research studies which are recommended in this preliminary report.

DEFINITIONS

The "hyperkinetic behavior syndrome" refers to a complex group of problems, occurring primarily in children, which are manifested in a manner extremely distressing to families and teachers, and to children themselves. This type of disturbance, which is also called "minimal brain dysfunction" (MBD), hyperkinetic syndrome, or hyperkinesis has no known single cause or simple answer for such problems. The major symptoms are an increase of purposeless physical activity and a significantly impaired span of focused attention. The inability to control physical motion and attention may generate other consequences, such as disturbed mood and behavior within the home, at play with peers, and in the schoolroom.

In its clear-cut form, the overt hyperactivity is not simply a matter of degree of activity but of quality or type of physical motion. The physical activity appears driven, so that the activity is beyond the child's control, as compared to other children. The child is readily distracted, racing from one idea and interest to another, but unable to focus attention. The Diagnostic and Statistical Manual of the American Psychiatric Association classified these disorders as:

IX. BEHAVIOR DISORDERS OF CHILDHOOD AND ADOLESCENCE (308)

308* Behavior disorders of childhood and adolescence

(Behavior disorders of childhood)

*This major category is reserved for disorders occurring in childhood and adolescence that are more stable, internalized, and resistant to treatment than transient situational disturbances (q.v.) but less so than Psychoses, Neuroses, and Personality disorders (q.v.). This intermediate stability is attributed to the greater fluidity of all behavior at this age. Characteristic manifestations include such symptoms as overactivity, inattentiveness, shyness, feeling of rejection, overaggressiveness, timidity, and delinquency.

308.0* Hyperkinetic reaction of childhood (or adolescence)

*This disorder is characterized by overactivity, restlessness, distractibility, and short attention span, especially in young children; the behavior is caused by organic brain damage, it should be diagnosed under the appropriate non-psychotic organic brain syndrome (q.v.).

The working revision of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-III) has changed the emphasis from hyperactivity per se, as the core symptom of the hyperactive reaction of childhood (308.0), to attentional deficits as the central component of this disorder; c.s. attention deficit disorder (314.00) with or without hyperactivity.

DIAGNOSIS OF HYPERKINETIC DISORDERS

In the diagnosis of hyperkinetic behavioral disturbances, it is important to note that similar behavioral symptoms may be due to other illnesses or to relatively simple causes. Essentially healthy children may have difficulty maintaining attention and motor control because of a period of stress in school or at home. It is important to differentiate the hyperkinetic child from

the child whose inattention and restlessness may be caused by hunger, poor teaching, overcrowded classrooms, or lack of understanding by teachers or parents. Frustrated adults reacting to a child who does not meet their standards can exaggerate the significance of occasional inattention or restlesness. Above all, the normal ebulience of childhood should not be confused with the very special problems of the child with hyperkinetic behavioral disorders.

The diagnosis of hyperkinesis is clearly best made by a skilled observer. Unfortunately, there is no single diagnostic test. Accordingly, the specialist must comprehensively evaluate the child and assess the significance of a variety of symptoms. Casual and contributory factors, both permanent and temporary, such as environmental stress, must be considered. Special dysfunctions such as certain epilepsies, schizophrenia, depression or anxiety, mental retardation or perceptual deficiencies must be distinguished. The less severe and dramatic forms of hyperkinetic disorders also require careful evaluation. Adequate diagnosis may require the use not only of medical, but os special psychological, educational and social resources.

PREVALENCE

Estimates of the prevalence of the hyperkinetic syndrome have ranged from a conservative estimate of 3% to a high estimate 1f 15% (Schrag, P. and Divoky, D. The Myth of Hyperactive Child, Pantheon Book, 1975, p. 35).

The most frequently cited prevalence estimates are given as ranging between 5-10% (Wender, P. Minimal Brain Dysfunction in Children, Willy & Sons, 1971, p. 62). In reviewing studies related to the 5-10% prevalence estimate, Wender has drawn from data obtained by Hussy, Prechtl and Stemmer, Stewart, et al, and from a survey done in Montgomery County, Maryland.

A conservative estimate would be that moderate and severe hyperkinetic behavioral disorders are found in about 3 out of 100 elementary school children--an estimate that would vary somewhat in different communities. (Report of the Conference on Use of Stimulant Drugs in Treatment of Behaviorally Disturbed Young School Children.) More males than females are affected, as is true in a number of childhood ailments.

Children with the hyperkinetic syndrome are clinically defined as limited to those of at least low normal or high intelligence. A near majority are reported to have had behavorial problems since infancy. There is a smaller group of more severely afflicted children upon whom most studies have focused: they may show hyperactivity and reduced attention which ranges in degree from mild to severe, with or without associated physical signs or special learning impairments; some have complex behavioral and personality problems. A significant number of hyperkinetic children have special learning and reading difficulties, along with the major hyperkinetic symptoms.

The range in prevalence figures reported could reflect actual differences in the populations studied or a number of other factors, including difference in socioeconomic status, geography, definitions and terminology from study to study, and any bias or selection by the investigator collecting the data. Details concerning these factors and their effect of estimates of pre valence have been provided by Minskoff, J. G., in Differential Approaches to Prevalence Estimates of Learning Disability. Annals. of the New York Acad. Sciences 205: 139-145, 1973.

Just as the estimates for the prevalence of the hyperkinetic syndrome have varied, so too have the estimates of the prevalence of the use of medication for the treatment of this disorder. In this regard, estimates of the prevalence of medication have ranged from 2% (Krager, J. M. and Safer, D. J., Type and Prevalence of Medication Used in Treatment of Hyperactive Children, New Eng. Jour. Med. 291:118-1120) to 2-4% (Sprague and Sleator, Pediatr. Clinics of North America, 1973) to a high of from 10-15% (in some school districts) as cited by Walker (Walker, S., Drugging the American Child; We're too Cavalier about Hyperactivity. Psycol. Today, Dec. 1974). It seems clear that the more conservative prevalence estimate of 2-4% of school age children as receiving medication for the treatment of the hyperkinetic syndrome represents the more valid national estimate.

FACTORS RELATED TO HYPERKINETIC DISORDERS

The present state of scientific literature indicates the perplexing problem of identifying definitive causes. The disorder has been ascribed to biological, psychological, social or environmental factors, or a combination of these. There is speculation that the core set of symptoms, i.e., those affecting control of attention and motor activity, may have their origin in events taking place before the child is born, during the birth process, or they may be related to some infection or injury in early life.

The hyperkinetic syndrome was originally described in children who had suffered known injury to the brain (Strauss and Lehtinen). Previously normal children who experienced severe physical trauma, or encephalopathy due to measles or influenza, for instance, sometimes afterward displayed disinhibited overactive behavior, stimulus-binding, and attentional defects.

That the converse is necessarily true, that all children who show any or all such symptoms must have experienced damage to their brains, is clearly contrary to logic. In fact, there is almost no information available on this possible relationship between neuropathologic changes of the sort identifiable by current techniques, and hyperkinetic behavior disorders except in rare and specific situations. The neuropathologic basis of the hyperactivity syndrome is simply unknown.

However, a discussion of some of the observed relationships between the occurrence of hyperactivity in children and social, environmental and biochemical factors, nutritional status, allergy or intolerance to substances, and exposure to toxic substances may contribute to our understanding of various components of the hyperactive child syndrome.

A. Social Factors: Almost all those who have discussed the etiology of deviant behavior syndromes assign importance to social aspects of the child's environment. The child's relationship with parents, teachers, siblings, peers and the culture at large are unquestionably significant contributors to his or her behavior, whether it be viewed as within or outside normal limits. Tensions arising from poor social relationships can trigger hyperactive behavior which in extreme form can contribute to further deterioration of the social input in a depressing downward spiral familiar to many teachers and parents. As mentioned earlier in this report, however, caution must be exercised in employing simple unimodal explanations of the effects of increased activity on socialization. Patterson, G. R., Jones, R., Whittier, J. and Wright, M. A. A behavior modification technique for the hyperactive child (Behav. Res. Ther., 1965, 2: 217-226) have proposed that a curvilinear relationship exists between activity levels and acquisition of socially acceptable behaviors, with moderate to high levels of activity correlating with social success.

Many workers have described significant success with social-behavioral approaches to treatment, and some insist that behavioral intervention is either universally effective or at least the most successful approach (Gelfand, D. M. and Hartmen, D. P. Behav. Therapy with Children, A review and evaluation of research methodology, In Graziano, A. M. (Ed) Behavior Therapy with Children, 1971, Chicago, Ill., Aldine Pub. Co.). Better results may be obtained when the entire family, teachers and peers are included in such interventions, again emphasizing that the social context in which the hyperkinetic child lives and grows is crucial. Even though an exclusively social-behavioral view of hyperkinetic behavior is undoubtedly incomplete (and at variance with data considered in other sections of this report) an awareness of this fundamental truth must permeate all discussions of causes, model mechanisms, and treatment interventions in relation to hyperkinetic behavior.

Food, nutritional status, and dietary intervention have significant familial and social components (Kallen, S. J. ed. Nutrition, Development and Social Behavior - USDHEW, PHS, DHEW Publication No. (NIH) 73-242). Introduction of special diets for a member of the family creates changes in the social interactions of members of the family. With regard to hyperkinetic children, it has been repeatedly pointed out that the child welcomes diet intervention and reminds other family

members of the importance of food restrictions to his behavior. (Stroufe and Stewart, L. A. Stroufe and M. A. Stewart, Treating Problem-Children with Stimulant Drugs, New Engl. J. Med. 289: 407-413, 1973), have described some of the changes in family structure that may occur during drug therapy for hyperkinesis: the child is less responsible for his own behavior and the parent avoids a degree of child-rearing responsibility.

B. Biochemical Factors: Hyperkinetic behavior is described as an aspect of many neuropsychological disorders. It is important to distinguish hyperkinesis from other aspects of these disorders, because they may involve separable biochemical dysfunctions and may respond to different pharmacological management. Hyperkinetic behavior may be associated with actual brain damage, as in perinatal anoxia and in the disorders described consequent to the 1917-1918 epidemic of encephalitis. In experimental animals, increases in spontaneous motor activity result from selective electrolytic and chemical lesioning, prenatal x-rays, and neonatal carbon monoxide exposure. The diversity of experimental treatments which produce hyperactive animals has complicated biochemical interpretations.

Briefly, two biochemical hypothesis for hyperkinesis have been proposed: (1) biochemical pathways of arousal are not functioning normally and hyperkinetic children are actually

underaroused or (2) biochemical pathways of behavioral inhibition are not functioning fully.

The first hypothesis is supported by the expected action of the amphetamines and methylphenidate to increase behavioral arousal. If it is correct then hyperkinetic children would be predicted to demonstrate underarousal biochemically and physiologically. There are reports of indicators of underarousal in such children -- such as galvanic skin response, auditory evoked response, and sleep EEG. So far, however, no differences have been found between hyperkinetic and normal children in levels of some urinary catecholamine metabolites or serotonin function in platelets or in rate of metabolism of the amphetamines.

A problem with this hypothesis has been that experimentally increased motor activity is associated with increased neurochemical function of catecholamine pathways linked to behaviorial arousal and those pathways are also stimulated by amphetamine and methylphenidate.

The second hypothesis of decreased function of pathways linked to behavioral inhibition has not been extensively investigated.

C. Nutritional Factors: One facet of biochemically induced hyperactivity is probably associated with many diverse influences related to nutritional factors. Such an influence

can, in some instances, be related directly to the quality and/or the quantity of bioavailable nutrients in the diet, or to the time relationships of the available supply of specific nutrients in response to the body's demand for nutrients and energy under the various circumstances of daily activity. In some instances, metabolic patterns differ substantially from individual to individual and as such, may increase the susceptibility of a particular individual to an excess of one factor or a deficiency of another.

The subsequent discussion on the possible role of food components in modification of neurological or behavioral changes should be prefaced by several considerations. A portion of the behavioral aberration in hyperkinesis may be dependent on psychological rather than metabolic or biochemical factors; however, given the primitive state of knowledge about this condition, metabolic abnormalities as causative factors in hyperkinesis remain distinct possibilities. Metabolic abnormalities may be of either a quantitative or qualitative nature. The pathways of metabolizing certain compounds may be essentially normal in the hyperkinetic child, but the quantities of compounds needed to produce a specific effect may be substantially higher or lower than those needed by the vast majority of the population.

Thus changes in levels of a stimulant such as caffeine might have little effect on normal people but could produce pronounced behavioral changes in hyperkinetic subjects. Qualitatively, there may simply be alternate metabolic pathways present in the hyperkinetic child that result in formation of abnormal products from precursors that are in no way harmful to the normal population.

Alterations in food intake can involve changes in the level of ingestion of a number of food constituents that have potential effects on neurological function, or on behavior. Food constituents may show these influences through deficiencies of nutritionally required constituents or through excesses of these or other components.

It has been hypothesized that diet can affect brain neurotransmission by altering the availability of precursors. These precursors, the amino acids tryptophan (precursor for 5-hydroxytryptamine) and tyrosine (precursor for norepinephrine and dopamine) and choline (precursor for acetylcholine) are normal constituents of dietary protein.

The evidence for dietary control of the rate of synthesis of the monoamines and acetylcholine to which they are converted comes from the work of Wurtman, et al., (Wurtman, R. J., and Fernstrom, J. D., Nutrition and the Brain in the Neurosciences 3rd Study Program, ed. by Schmitt, F. O., and Worden, F. G. pp. 685-693, MIT Press, Cambridge, 1974): (Wurtman, R. J.,

Catechol Synthesis: Control by Brain Tyrosine Concentration, Science 185: 183-184, 1974); (Wurtman, R., Abst. 5th Annual Mtg. Soc. Neuroscience, 1975).

For example, peripheral administration of tryptophan or tyrosine to rats increases the amount of these substances in the brain, and results in a significant increase in the rate of synthesis of brain 5-hydroxytryptamine and catecholamine (norepinepherine and dopamine), respectively. It has also been shown that it is not only the absolute amount, but also the relative proportion of these amino acids in the diet which determine their effect on monoamine synthesis. More especially, amino acids which compete with tryptophan and tyrosine for uptake into the brain can lower their entry into the brain and thus decrease 5-hydroxytryptamine and catecholamine synthesis, respectively. (The amino acids, i.e. tryptophan, tyrosine, phenylalanine, leucine, isoleucine, and valine, share a common uptake system and thus compete with each other for entry into the brain.) Thus, the amounts of any of these amino acids in the diet (and also any other dietary factors which can alter endogenous amino acid levels) can influence brain monoamine synthesis.

Other agents, such as administration of insulin (2 units/kg) or consumption of a carbohydrate meal by rats, which has

been found to cause an increase in plasma tryptophan, and a decrease in levels of other amino acids, results in an increased level of brain tryptophan and 5-hydroxytryptamine. (Wurtman, R. J. and Fernstrom, J. D. Nutrition and the Brain in the Neuroscoeiences 3rd Study Program, ed. by Schmitt, F. O. and Worden, F. G., pgs. 685-693. MIT Press, Cambridge, 1974).

Other dietary factors can indirectly influence the availability of precursor amino acids for brain monoamine synthesis. This is especially true for free tryptophan, which is transported in the blood loosely bound to plasma albumin. (Paoletti, R., Sirtori, C., Jr., and Spano, P. F. Clinical Relevance of Drugs Affecting Tryptophan Transport, Ann. Rev. Pharmacol. 15: 73-81, 1975).

Since free fatty acids (FFA) are also bound to plasma albumin, they can displace the free tryptophan that is not chemically bound, from the plasma albumin, and any dietary factor leading to altered FFA levels can potentially alter the amount of tryptophan available for entry into the brain and conversion of 5-hydroxytryptamine. For example, the decreased FFA levels induced by glucose ingestion in humans decreased the percentage of free tryptophan by about 35%. Interestingly, all stimulant drugs used in the treatment of the hyperkinetic syndrome, including caffeine, has been shown to increase serum or plasma FFA in animals and/or man, and the administration of amphetamine to animals has been

shown to produce up to a 3-fold increase in brain tryptophan levels. Parenthetically, it may be mentioned that salicylates are also capable of displacing tryptophan from albumin. (Paoletti, R., Sirtori, C., Jr., and Spani, P. F., Clinical relevance of Drugs Affecting Tryptophan Transport. Ann. Rev. Pharmacol. 15: 73-81, 1975).

The practical effect on human behavior of altered brain monoamine synthesis due to dietary factors which alter the availability of precursors for monoamine synthesis is difficult to assess. Relatively large doses of monoamine precursors have been used with variable success in treating depression, (Carroll, B. J., Monoamine Precursors in the Treatment of Depression. Clin Pharm Ther. 12: 743-761, 1973), although relatively large doses were used. The administration of large doses of tryptophan is being investigated for use as a soporific, and for treatment of MBD.

In addition to direct effects on neurotransmitter levels, the presence or absence of food components may produce a number of neurological or behavioral effects. The mechanism of these is relatively less clearly understood. For example, deficiencies of many of the B-complex vitamins produce effects on the central nervous system and on behavior, possibly through their role as coenzymes. Also not clearly

understood are the role of trace minerals such as manganese, copper, zinc, or iron in altering behavior. However, it is known that behavioral changes develop with iron deficiency anemia that are readily reversed on treatment with iron. (Read, S. M., Anemia and Behavior, Mod Prob. Pediat. 14:89-202, 1975). Manganese deficiencies in animals is associated with control of motor activity. (Hurley, L. S. and G. J. Everson, Proc. Soc. Exp. Biol. Med., 102:360, 1959).

The influence of these dietary factors may occur in several ways:

1. Direct dietary deficiency as in iron, manganese, copper or zinc. It is known that the diet in the U. S. can easily be deficient in zinc and iron unless foods are selected with substantial care.
2. An abnormally high requirement of some children for certain vitamins such as niacin, folic acid or pyridoxine. Niacin and pyridoxine are normally present in the diet in quantities adequate for most of the population. The adequacy of folic acid in the diet of some of the population is open to question.

3. Abnormal metabolism of any of these vitamins or minerals in a manner that effects chemicals which regulate behavior.

Metabolically induced hyperactivity has also been linked to the occurrence of hypoglycemia. In those individuals who are susceptible to reactive (post absorptive) hypoglycemia, the relative proportions of energy yielding nutrients can affect the occurrence of symptoms. In these individuals diets high in carbohydrates, especially for breakfast meals, promote hypoglycemic symptoms which include hyperactivity, irrationsl behavior, and inability to concentrate, (William, R. H. Textbook of Endocrinology, W. B. Sanders Co., Phila. Pa. p. 640, 1974).

The occurrence of such symptoms can be avoided by the consumption of diets high in protein and fat relative to carbohydrates. That the condition is influenced by the con sumption of high levels of carbohydrates is shown by the fact that the symptoms are frequently avoidable during fasting. The assumption is that the absorption of carbohydrates stimulate the secretion of insulin in either excessive amounts or that such insulin is not subjected to normal metabolism. In either case, the levels of insulin remain high after blood glucose levels have returned to a normal range. Subsequent reduction of blood glucose results in

the occurrence of hypoglycemia symptoms. Stimulation of catecholamine secretion is beneficial to such individuals in that insulin levels are lowered and the utilization of glucose by the muscles is reduced.

D. Allergy or Intolerance to Substances: Unusual reactions to many substances may induce hypersensitivity or an intolerance phenomena. These inducing factors may include biochemical entities which are ingredients present in the foods themselves, or natural or artificial ingredients which are added to other foods as agents to aid in the processing, flavoring, coloring or preservation of foods. Such natural or artificial ingredients are generically referred to as food additives. The phenomena induced may range from demonstrable antibody-mediated allergic reactions to the less well understood intolerance phenomena which reflect non-antibody-mediated manifestations more properly characterized as toxicity reactions. Physical manifestations of such phenomena may include obvious signs of eczema, urticaria, asthma, etc., to less obvious manifestations which can include malaise, fever, and neurobehavioral changes.

A relationship between an allergic or hypersensitive reaction to artificial food additives and hyperkinesis has been postulated by Feingold. However, while a variety of allergic or sensitizing reactions ranging from urticaria (hives) to

severe asthma have been reported to occur in susceptible people following ingestion of certain synthetic colors that are used in foods and drugs (Chafee, F. H. and Settipane, G. S., 1967, J. Allergy 40:65; Feingold, B. F., 1968, Ann. Allergy 26:301: Lockey, S. D., 1959, Ann. Allergy 17:719; Samter, M. and Beers, R. F., 1967, J. Allergy 40:281), there is presently no evidence to indicate an association between an allergic or hypersensitive response to these agents and hyperkinesis. The mechanism of hypersenitivity to aspirin is not well understood. Because aspirin is a low molecular weight compound, its sensitization effect has been postulated to be that of an incomplete antigen or hapten. The hapten is a chemically active substance of low molecular weight that does not induce an immune response by itself but by combining with larger molecules called "carriers" becomes immunogenic (Sell, S. - Immunology, Immunopathology, and Immunity - Harper and Row, New York, 1972). Most of the patients studied were persons showing allergic or sensitivity reactions to acetyl salicylate. Aspirin intolerance has not been found consistently to be generalized to salicylate intolerance since many aspirin intolerant patients do not react to sodium salicylate, salicylic acid esters, choline salicylate, or thioaspirin (M. Samter, Hosp. Prac. 85-90, 1973). Of Samter and Beers' 182 aspirin sensitive patients with asthma and sometimes urticaria, approximately 23% had

sensitivities to foods and drugs. Fourteen patients were found to be sensitive to the dye tartrazine. Similar findings of tartrazine have been reported by other investigators although the percent of aspirin sensitive persons who are sensitive to tartrazine has been reported as greater than that seen in the initial series (Juhlin, M., Michaelsson, G., and Zetterstrom, O.-Urticaria and Asthma Induced by Food-and-Drug Additives in Patients with Aspirin Hypersensitivity, J. Allergy and Clin. Immunol. 50:92-98, 1972). Cross reactivity of aspirin sensitivity persons has been reported with benzoates (Chaffe, E. H. and Settipane, G. S.: Asthma Caused by FD&C Approved Dyes, J. Allergy 40:65, 1967), although this is much less frequent than cross-reactivity to tartrazine (Anonymous Aspirin Intolerance - Lancet, Annotations, Sept. 14, page 618, 1968).

Cross reactions have been reported for other azo dyes and benzoates (G. Michaelsson and L. Juhlin, Urticaria Induced by Preservatives and Dye Additives in Foods, Br. J Dermatology 88: 525-532, 1973). The mechanism responsible for the cross-reactivity of aspirin, tartrazine and other azo dye sensitivity or intolerance is not established.

Tartrazine, if taken orally, undergoes azo-reductive cleavage in the gastrointestinal tract and in humans results in the excretion in 48 hours of sulfanilic acid equivalent to

the total amount of tartrazine ingested. (Jones, R., Ryan, A. J., and Wright, S. E.: The Metabolism and Excretion of Tartrazine in Rat, Rabbit, and Man) Food Cosmet. Toxicol. 2:447, 1964).

Samter and Beers have suggested that tartrazine undergoes biotransformation in a limited number of persons which may account for sensitivity reactions in a small number of persons (Samter, M. and Beers, R. E.: Concerning the Nature of Intolerance for Aspirin - J. Allergy 40:281-293, 1967).

Because of the possibility that an in vivo formed metabolite of the food additive is responsible for the hypersensitivity response sublingual or cutaneous testing with the compound may yield false-negative results. It is also possible that physical alterations of foods during processing or cooking may produce a change in the structure of the additive and be responsible for false-negative results on testing of the unchanged additive.

Because of the difficulties of determining food allergies with subcutaneous and sublingual testing, elimination diets and challenges with the food or food component in question are tried by clinicians. These trials are basically very similar to many of the studies proposed to evaluate the effects of food colors and flavors on hyperkinesis.

TOXIC REACTIONS

The influence of food on neurological functions or behavior can occur through chemical constituents present in food other than those nutritionally required. There are a number of psychoactive components in foods such as nutmeg or ergot, which may be consumed by eating food contaminated with a fungus. In susceptible individuals substantially smaller quantities of these compounds than are usually required may produce central nervous system effects.

Lead Toxicity: Research on lead toxicity in children has demonstrated involvement with both the peripheral and central nervous system. Through the years, this area of research has been intensely investigated and the literature has been the subject of two recent reviews (Wiener G. Varying Psychological Sequelae of Lead Ingestion in Children, Public Health Rep., 85: 19, 1970, and Waldron, H. A. and D. Stofan, Subclinical Lead Poisoning, New York Acad. Press, 1974). Among the symptoms observed in individuals who contracted lead toxicity during childhood are hyperactivity, impaired learning, heightened aggressiveness, emotional instability and deficiencies in motor coordination. These changes in central nervous system function appear to be permanent. However, some have responded to drug therapy and there is some evidence that treatment with

chelating compounds was useful. The impact of subclinical lead toxicity on learning and behavioral disorders has been studied. (Moncrieff, A. A., et al., Lead Poisoning in Children, Arch. Dis. Child, 39:1, 1964 and Millar, J. A., et al., Lead and α-Amino-levulinic Acid Dehydratase Levels in Mentally Retarded Children and in Lead-Poisoned Suckling rats. Lancet II: 695, 1970).

The results of these studies are not conclusive and comparisons are difficult due to methodology differences. Epidemiological data on the other hand have shown correlations between lead poisoning and hyperactivity, deficits in motor coordination and learning. (De La Burdee, B., Does Asymptomatic Lead Exposure in Children have Latent Sequelae? J. Pediat. 81: 1088, 1973 and David, O., Lead and Hyperactivity, Lancet I:900, 1972.)

A review of data published in the literature shows that lead toxicity has a significantly greater impact on the very young (less than six months of age) compared to older children. (Belmont, L. and H. C. Birch. The relationship of time life to behavior consequence in brain damage: The organizational of factual form experience in brain injured adults, J. Nerv. & Men. Diseases, 137: 489, 1960; Airborne lead in perspective, Washington, D. C., National Academy of Sciences, 1972 and Greensbaum, J. V. and L. A. Laurie, Encephalitis as a Causative factor in behavior of disorders of children, JAMA 136:923, 1948).

SAFETY TESTING OF FOOD ADDITIVES

Throughout history humans have ingested a variety of dietary substances either for their intrinsic nutritional value or for the purposes of enhancing appearance, flavor, preparation or preservation of foods. These included condiments, spices, pepper and salt.

Natural coloring and flavoring agents were used in food products until such time as their supply became limited in relation to demand. Chemists, then asked to provide cheaper substitutes, analyzed the complex chemistry of flavors to determine characteristic moieties which could be isolated or synthesized and combined to reproduce the flavor desired. Natural substances were first used as coloring agents and included calcium carbonate, charcoal and vegetable extracts. When organic dyes were found which would mimic reds, blues, yellows and greens, they gradually came into use.

In the United States prior to 1958, pre-clearance for food and color additives was not mandated. While the Food, Drug and Cosmetic Act of 1938 prohibited the addition of poisonous or deleterious substances to food, the lack of pre-clearance requirement imposed upon the Food and Drug Administration the responsibility to determine whether a food additive was harmful. This was done only when there was an indication that the additive might be harmful. In the case of the synthetic organic colors (so-called coal tar colors) the law mandated that FDA test these colors for their ability to cause harm and that FDA establish certification procedures for these colors on a batch basis. A number of such colors were removed from use. In essence then, prior to 1958, the FDA was required to establish that

compounds were harmful on the basis of legally satisfactory evidence before they could be removed from use.

The food and color additive amendments of 1958 and 1960, respectively, changed the legal philosophy. Pre-clearance was required. This shifted responsibility to the user for the prior establishment of safety. These amendments also set forth the principle of "safe conditions of use". This, in essence, was recognition of the generality that any chemical (even those which are essential to life and not considered to pose any hazard) may be unsafe, unless used under conditions which are proper for its safety. The food additive amendment contained a "grandfather" clause which in effect, without the need for pre-clearance, permitted those food additives that were in actual use prior to January 2, 1958, and which were Generally Recognized as Safe [GRAS] or were considered safe on the basis of scientific procedures or long experience of use to continue in use. The 1960 color additive amendments, while requiring safety testing for all colors, recognized the need and provided for an interim listing of colors commercially established at the time of enactment of the law, with the proviso that this would not apply to those colors subject to certification for which no batch had ever been certified and further, that for any color listed on an interim basis safety studies were to be initiated promptly, evidence to this effect being required within two and one-half years.

During the period of time (1958-1960) and subsequently until 1970, FDA was confronted with a series of pragmatic problems involving priorities for resolving problems on a "worst first" basis, in

view of limited resources. It was recognized that there were countless hundreds of "additives" and food ingredients that had enjoyed a long history of apparent safe use.

The GRAS list, created after review by toxicologists nation wide, established those additives which were considered as being safe without further safety testing for their intended use. This permitted FDA to concentrate on potential problem substances, not considered GRAS, many of which become classified as food additives, for which additional safety evidence was demanded and received before FDA could grant approval for use.

For the past few years, FDA has funded a major safety review of substances on the GRAS list by a select committee of the Federation of American Societies for Experimental Biology, to determine if additional safety evidence is needed or if restrictions on currently permitted uses are indicated. Currently underway is a similar review for flavors.

In general, safety testing depends upon the fact that as the exposure dose is decreased, toxicity effects also decrease and a dose is finally established at which "no effects" are produced. Usage levels which are permitted in food are then set based on the "no-effect" level into which has been incorporated an additional safety factor.

To some extent the kinds of safety data required by a preclearance review to establish the safety of a proposed food or color additive are also directly related to the anticipated degree of human exposure likely to result if such use is permitted. For

significant direct additives, i.e., those which are intentionally added to food, complete toxicological workup is required. For indirect additives, i.e., those which have some potential for transfer into foods by virtue of their use in the manufacture or maintenance of food packaging materials and processing equipment, toxicity testing requirements may be reduced. In particular, only short-term animal testing might be required to determine if a substance was highly toxic where essentially no residues from migration or extraction is expected to occur in food.

At present, a complete toxicological workup includes a variety of chemical tests to determine the composition and purity of the substance in question and then a variety of feeding experiments in test animals to determine the quantitative strength of all qualitative toxic effects that the substance can be demonstrated to cause in animals receiving large doses daily over extended periods of time. For example, lifetime feeding studies are required in two different rodent species - usually the mouse and the rat. These tests are designed to establish an "effect" level, if possible. FDA looks for a variety of effects such as poor growth and development, visible signs of neurological abnormalities, including those likely to be associated with chemically-induced lesions on the motor and sensory centers and pathways of the nervous system. Animals are observed for abnormalities of gait, righting reflexes, ingesting reflexes, and tremors. They are also observed for any other visible palpable signs of disease such as skin, ear and eye abnormalities, gastrointestinal disturbances, and tumors. After death, the animals are

subjected to a complete autopsy and extensive histopathological examination to determine cause of death, compound related diseases, and any incidence of tumors including malignant neoplasms (cancer). The data are then analyzed statistically when differences between test and control animals are seen, to determine the statistical significance of those observed differences. One rodent lifetime study, the rat study, is designed so that the animals used have been exposed to the test material over their lifetimes beginning with exposure in utero. This insures that they have been exposed to any substance likely to cross the placenta. In multi-generation studies, parents of successive generations are observed for reproductive performance, fertility and viability and growth of offspring. Successive mating serves to determine whether offspring who were exposed in utero are capable of reproducing their own normal offspring. These multi-generation reproduction studies (usually on the rat) usually involve two litters per generation over three generations.

Other specific tests, such as teratology studies, are performed to see if a substance can be demonstrated to be capable of inducing birth defects. Reproductive testing, in general, will detect decreased fertility, increased fetal death, birth defects, decreased survival and well-being of offspring at birth after being exposed in utero; and abnormal growth and development during the lactation stage with the maternal animals still exposed to the test substance. These required reproduction protocols will obviously measure effects of the substance tested on the entire spectrum of physiological

functions involved with the maternal animals still exposed to the test substance, and on the entire spectrum of physiological functions involved with reproduction. The physiology of reproduction involves the integration of complicated metabolic, hormonal, neurological and behavioral processes and thus serves also to detect more subtle disturbances of higher centers.

TREATMENT PROGRAMS

Although the symptoms of hyperkinesis in children may range from mild to severe and have poorly understood causes and outcomes, the need for treatment or special interventions remains.

Several approaches to treatment now appear to be helpful. Special classes and teachers can be directed to specific learning disabilities and thus restore the confidence of the child who experiences chronic failure. Modification of behavior by systematic rewarding of desired actions has been reported to be useful in some children. Elimination of disturbing influences in the family or classroom through counseling may often tip the balance, and a happier child may show improved control and function.

Drugs: There will be children for whom efforts such as those described above are not sufficient. Their histories and their examinations reveal symptoms of such a driven nature that skilled clinicians undertake a trial of medical treatment. Drugs do not "cure" the condition, but the child may become more accessible to educational and counseling efforts. Over the short term and at a critical age, medication can provide the help needed for the child's development.

Stimulant medications are beneficial in only about one-half to two-thirds of the cases in which trials of the drugs are warranted. The stimulant drugs are considered to be the first and least complicated of any drugs to be tried. Other drugs, such as the so-called tranquilizers and anti-depressants, are generally reserved for a smaller group of patients. Without such specialized medical therapy, the developmental and educational consequences for these children are

clearly severe. In such cases the aim is not to "solve problems with drugs," but to put the severely handicapped child in a position to interact with his environment to the extent that his condition permits.

Response to stimulant medication cannot be predicted in advance. Fortunately, the issue can be resolved quickly. When stimulants are given in adequate doses, a favorable response occurs fairly rapidly, and is unmistakeably the consequence of the drug. Thus, if an adequate test of pharmacotherapy (a few days or weeks) produces only doubtful benefits or none at all, treatment can be promptly terminated. The physician will, of course, adjust dosage carefully to assure an adequate therapeutic trial. It should be pointed out, however, that not all affected children require medication and that of those who do, not all respond.

When the medication is effective, the child can usually modulate and organize his activities more in the direction he wishes than previously. The stimulant does not slow down or suppress the hyperkinetic child in the exercise of his initiative, nor does it make him feel overstimulated, or out of touch with his environment. Although their exact mechanism of action is not known, stimulants do not provide a chemical strait-jacket. They do not act as a sedative. Rather, they appear to mobilize and to increase the child's abilities to focus on meaningful stimuli and to organize his bodily movements more purposefully.

The most typical side-effects of the stimulant medications, loss of appetite and sleep difficulty, diminish over time and can be adequately controlled by adjusting the prescribed dosage and/or the time

during the day when the drugs are given. No medication should be given for a longer period of time than may be required and it is good clinical practice, therefore, to discontinue medication for a few weeks once or twice a year to determine whether or not the child still requires medication. If there is no recurrence of the symptoms of the hyperkinetic syndrome, medication should be discontinued. In a recent long-term study of methylphenidate, it was reported that 26% of 60 MBD children no longer required medication after two years of treatment. (Sleator, K. von Neumann, A. & Sprague, R. C. "Hyperactive Children: A continuous long-term placebo controlled follow-up." JAMA, 229: 316-317, 1974).

DIETARY INTERVENTION

Dr. Feingold has recently suggested that the occurrence of hyperkinesis and learning disabilities in school age children, irritability, sleeplessness, restlessness and crying in young children and colic in infants, are linked to the ingestion of artificial food colors and flavors. In testimony before the Senate Subcommittee on Health, he has indicated, "Following management (of children whose primary complaint was hyperkinesis or MBD) with a diet eliminating all artificial colors and flavors, we again observed the rapid and dramatic responses in about 50% of cases as reported by our earlier patients. Within a few weeks and sometimes within a few days, a complete reversal of the behavioral pattern was observed."

It must be recognized that the Feingold treatment constitutes more than just the elimination of food colors and food flavors from the diet. In this regard, it should be stressed that:

1) Any diet provides a general nutritional change for the person following the diet.

2) Any treatment intervention initiated to help the patient carries with it definite expectations on the part of the healer and on the part of the patient that improvement will follow from treatment. Non-specific therapeutic improvement (placebo response) is usually observed by the physician, parent, and patient. The Feingold regimen requires a marked change in the family diet and consequently a change in the social interaction of the entire family with the hyperactive child. Thus, fairly strong non-specific

therapeutic changes would be anticipated.

3) Finally, if the Feingold diet eliminates artificial food colors and flavors, then this specific aspect of the diet may be responsible for any observed therapeutic improvement. It should be emphasized that this attribution of specific therapeutic improvement to the elimination of food colors and flavors constitutes only one aspect of the "Feingold" hypothesis. The reason for this emphasis stems from the design implications that follow from the hypothesis that is to be tested. Thus, to test the Feingold regimen implies a test of the general therapeutic change that follows from an admixture of the three components of the regimen that have been elucidated above, i.e., general nutritional changes, altered family social interactions, and the elimination of artificial food flavors and food colors.

In many respects, Dr. Feingold has conceptualized his hypothesis of an adverse behavioral response associated with artificial food flavors and colors as an age-continuum in sensitive children.

For example, he implicated food flavors in the vitamin drops of infants as responsible for the development of colic, and food colors and flavors in the 1-3 year age group as associated with crying, sleeplessness, motor restlessness and irritability. In school age children he implicates the presence of artificial food colors as underlying the behavioral syndrome which is frequently diagnosed as minimal brain dysfuncton or the hyperkinetic reaction of childhood and which includes such symptoms as poor attention span,

distractability, hyperactivity, irritability and specific learning disability.

The hyperkinetic syndrome is most frequently diagnosed during the early school years when the task demands placed upon the child in the classroom are most likely to magnify the core symptoms of the disorder, i.e., the inability to sustain attention and to inhibit motor activity. In retrospect, however, these children are typically described by their parents as being "difficult" children prior to coming of school age, i.e., characterized by crying, irritiability, excessive motor activity and emotional lability.

Looking forward in time from the early grammar school period, it seems clear that these hyperkinetic children are at greater risk for academic failure with associated patterns of "acting-out," being loners, emotionally immature, etc. (Weiss, B. Minde, R., Wery, J., Douglas, V. Nemeth, E., Studies on the hyperactive child, VIII, Five Year follow-up. Arch. Can. Psychiat. 24 1971). In all of this process, it is difficult to tease out the behaviors which may stem from initial nutritional causes from the behaviors which may stem from the typical kinds of destructive social interactions that these initial behaviors are likely to call forth from the child's parents, siblings, peers and teachers.

For example, the child who keeps his parents up all night is probably going to be treated somewhat differently than the child who places less of a strain on the emotional and physical resources of his parents. The child who is continually in motion is more apt to find himself in confrontation with his siblings and his peers. The

child in school who cannot sit still at his desk and do his school work without being a constant disruption to his classmates and his teacher is much more likely to be labeled as a "trouble-maker" and to develop and internalize a poor sense of personal worth than the child who is not so handicapped. The child who is incapable of sustained attention, despite an adequate IQ, is apt to experience continuous academic failure and is likely to develop a poor self-image. Such a child may turn to delinquent and/or sociopathic behaviors as a result of this labeling process, partly imposed by others and partly internalized as a result of his continuing experience of failing to measure up to his own expectations.

In essence, then, if some children, for whatever reasons, have an intolerance to certain dietary components, it is altogether possible that the symptoms of that intolerance may be manifested differently in different children, given the obvious overlay and interplay of psychosocial factors, personality factors and factors stemming directly from the severity of dietary intolerances or more general nutritional deficiencies.

In order to test the possible etiological relationship between food colors and food flavors and the various manifestations of the hyperkinetic reaction of childhood at different ages, it becomes most important to implement studies using different age groups of behaviorally impaired children who seemingly evidence a therapeutic response to the Kaiser-Permanente (K-P) regimen. By examining different, but age-appropriate components of the hyperkinetic reaction of childhood in relation to nutrition and/or nutritional intolerance,

it becomes possible to provide a more theoretically meaningful test of a longitudinal theory that may provide a causal understanding of the development of the hyperkinetic-behavior syndrome in at least some children with this very common behavior disorder of childhood.

REVIEW OF COMPLETED RESEARCH RELEVANT TO THE FEINGOLD HYPOTHESIS

Drawing from his clinical experience, Dr. Feingold has estimated that somewhere between 25-50% of children thought to be hyperkinetic evidence a dramatic therapeutic response to a special diet he has published which eliminates certain artificial food colors and flavors. This material comprises clinical observations and summaries of impressions from his patients and their personal milieu--parents, peers, and teachers. Among the observations are:

(1) the effect of dietary change on a variety of behavior disorders and on patients ranging in age from infants to adults;

(2) the equal therapeutic effect of the diet on children who fail to respond to stimulant medication and those who are responsive to stimulants;

(3) the purported ability of the diet to affect two aspects common to hyperkinesis; learning disabilities and behavioral impulsivity;

(4) the apparently short latency period between a single infraction of the K-P diet and the expression of behavioral dysfunction.

However, these reports do not constitute a scientific basis for determining the validity of the "Feingold" hypothesis. His writings describe the immense impact of dietary alteration upon the psychosocial dimensions of children classified as hyperkinetic. A clear separation of these two variables, change in dietary constituents and concurrent changes in parent-child relations, is required. Although Dr. Feingold maintains that it is the specific

change in dietary constituents (artificial colors & flavors) which produces behavioral improvement, he has not attempted to validate his hypothesis by separating these two components.

In one pilot study conducted by Wender, an attempt was made to investigate the effect of the Feingold diet on hyperkinetic children. The report from this study consists largely of impressionistic observations and no data has been presented to permit statistical analysis. Briefly, the study was conducted in two stages: (1) open screening to find from a group of subjects those who responded to the Feingold diet with behavioral improvement as measured by questionnaire and rating scale and (2) challenge of the "responders" with sodium salicylate or placebo. The concentration of the challenge phase of the study on salicylates reflected Dr. Feingold's past emphasis on salicylates.

Six of eleven children demonstrated an initial behavioral improvement. However, the report states that of the responders, five out of six showed a return to pre-diet behavior over the challenge period even though diet was continued. This deterioration of behavior was not related to dosage with placebo or salicylate. It may be interpreted to cast doubt upon the observation of initial improvement. The subjects and their evaluators (parents and teachers) were probably not blind, and first reports of improvement might reflect expectations or imprecise methods of evaluation. In addition, the study design did not sort out psychosocial effects, possible substantive nutritional change, and specific elimination of additives under the K-P diet. Further, the erratic changes in

behavior could be ascribed to infractions of the diet by the subjects. This possibility indicates the need for careful records of compliance.

A study by Conner represents an important preliminary attempt to investigate the Feingold hypothesis by a double blind crossover design. A double blind crossover trial involving a control diet and a diet eliminating artificial flavors, colors and natural salicylates (K-P diet) as recommended by Feingold was conducted on 15 children diagnosed in accordance with the American Psychiatric Association's definition of Hyperkinetic Reactions of Childhood. These children were randomly assigned to either the K-P diet followed by a control diet or to the opposite dietary sequence. Efforts were made to insure that neither parents, teachers, nor the investigator knew which diet the children were on during the experiment (double-blind). Efforts were also made to measure dietary compliance and to match the diets in terms of difficulty of preparation. Teachers and parents observed the children using a standardized symptom rating scale to monitor changes in the symptoms of the hyperkinetic syndrome.

Dr. Conner reports a statistically significant difference between the K-P diet and baseline measures on both parent and teacher ratings; no statistically significant difference between the control diet and the baseline measure; and a statistically significant difference between the K-P diet and the control diet based on teacher ratings, but no significant difference between the K-P diet and the control diet based on parent ratings. Clinical judgment ratings by the investigator also showed significant differences between the two treatments.

The investigator concludes that "the K-P diet may reduce hyperkinetic symptoms" but warns that "it would be hazardous at this point to draw too many conclusions from this experiment, given the small size of the sample and the lack of complete consistency in the results. Any thoughtful observer will understand that a major intervention into dietary habits of a family will produce behavioral effects, regardless of the specific diets, a phenomenon well understood in the management of such conditions as juvenile diabetes. The results would have been substantially clarified if it had been possible to have objective measures of function uncontaminated by the psychological factors which are bound to operate in the family-school-child system. At this point, the results point to the need for considerable further investigation."

The only other available study which has been completed is that conducted by Keithly in California in collaboration with Dr. Feingold. Nineteen hyperactive children were placed on the K-P diet for a period of two to three months. Parents and teachers completed a behavior checklist before the study began and at three-week intervals. Results revealed that parents' evaluations yielded significant gains in the pre-test compared to post-test population means. Notably, evaluations by teachers did not demonstrate significant changes. However, the validity of these findings is questionable in view of the lack of adequate control for dietary intervention and particularly the introduction of numerous biases. The biases occurred by exposing the parents and children to the anticipated outcome of the study before it began, by rewarding children for staying on the diet, and by

sending a letter of information to the teachers reflecting what beneficial effects may occur.

In specific terms of either proving or disproving the Feingold hypothesis, the limitations of the available studies conducted to date make them inconclusive. Feingold's original observations are anecdotal and not scientifically controlled or objective. None of the previous studies separated psychosocial changes from dietary intervention, did not adequately "blind" the evaluators, and did not differentiate nutritional change from specific elimination of certain food additives. The data from this last report are questionable primarily because of the biases introduced into the study.

A study at the University of Wisconsin which is currently underway and which will be completed in December, 1975, will provide data on a sample of 45 hyperactive children who participated in an eight-week trial (following a two-week period of baseline evaluation) contrasting the K-P diet with a control diet which includes the average amount of artificial food colors and flavors. A counterbalanced crossover design is employed and an extensive evaluation battery, including parent - teacher blind observer ratings, as well as objective attentional and learning tasks, was employed to assess therapeutic change.

These studies which have been reviewed to date have been of value in indicating the potential difficulties in testing the hypothesis. Statistical analysis becomes especially difficult since the small sample sizes have reduced the significance of all findings. Records of compliance are necessary, and this need raises questions

as to whether or not well-controlled outpatient studies can be accomplished. The identification of "responders" is not sufficient if blindedness is not preserved; no "challenge" study has incorporated artificial food flavors and colors to test specificity of responsiveness. Crossover designs may be confounded by loss of blindedness, and disturbing sequence effects should be investigated by either intensive designs using repeated crossovers and/or incorporation of a return to baseline after completion of each diet sequence.

MINIMUM DESIGN REQUIREMENTS FOR A DIETARY STUDY

Before proceeding to a more specific discussion of the issues involved in testing the Feingold diet/regimen, it is useful to examine the relevant criteria advanced by Sprague and Werry (1971) which are as follows:

1) Placebo control

2) Random Assignment of Subjects. Assignment of the subjects to experimental conditions should not depend upon the hunches or other idiosyncratic procedures of a particular investigator for this may seriously bias the sample. If, as is true in many cases in this review, some type of match-pair design is used, then the members of the pairs should be assigned at random to the conditions. If some type of crossover design (a common term in psychopharmacology that indicates a design in which each subject receives each experimental treatment) is utilized, then the subjects should be randomly assigned to the sequences of treatment used in the experiment. Furthermore, random assignment is necessary to meet the minimum assumptions of the statistical tests which should be used to evaluate the findings.

3) Double-blind (DB). This term simply means that neither the subject taking the medication nor the person evaluating the subject's behavior are aware of which is the placebo condition and which is the active medication condition. This procedure attempts to prevent the investigator's expectations from influencing his assessment of the subject's behavior, as well

as the subject's expectations.

4) Standardized Evaluations. By the term "standardized evaluation," it is meant that the measurement instrument has been used before and some empirical information on basic reliability (does the instrument give the same finding when repeated across testers and/or time) and validity (some independent evidence that the instrument is actually measuring what it purports to measure) is available. In addition, it is obvious that more rapid advance can be made if the measuring instrument is anchored in some good theory. (Standardized evaluations are given in the "Special Children's Issue" of the Psychopharmacology Bulletin; 1973).

5) Appropriate Statistical Analysis. It is not sufficient simply to list percentage figures about the degree of improvement in a drug or diet study. Such data are next to impossible to interpret operationally and are seldom subject to scientifically valid tests of replicability. The most acceptable manner of data evaluation is to use some kind of inferential statistical analysis. Mere use of statistics is, however, not sufficient, for they can be and are often grossly abused. An appropriate statistical analysis which does not violate the assumptions of the test used is necessary.

To these criteria, one might add the following additional considerations:

6) Careful Selection and Specification of the Patient Sample. The hyperkinetic child syndrome is difficult to define. It is

currently held that children so diagnosed are heterogenous with respect to possible etiologies and with regard to the specific constellation of symptoms and signs that are commonly accepted as comprising the disorder. Nevertheless, there is general agreement that this syndrome typically includes only children of low normal or higher IQ, without gross physical or neurological handicaps and who are not autistic, schizophrenic, primarily asocial, aggressive, or overanxious. Situational stress reactions are usually excluded by requiring a history of the disorder of a few years and by requiring that the child be perceived as trans-situationally hyperactive (i.e., judged as hyperactive by at least two classes of observers such as parents and teachers, parents and physicians, teachers and physicians). It may also be helpful to require a minimum severity score on the target symptoms of hyperactivity. Many investigators have employed this procedure and have required a score of at least 15 out of a total possible score of 30 on the hyperactivity factor of the Conner's Teachers Questionnaire (Conners, C.K., A teacher rating scale for use in drug studies with children. Amer. J. Psychiat., 126:152-156, 1969). Each subject should receive a physical examination to detect overt nutritional deficiency symptoms and an analysis of blood for iron, zinc, lead, ferritin, and RBC folate. In addition, a fasting blood glucose and a urinalysis for nicotinic acid should be accomplished. History of allergy involvement should be obtained by interview and, where available, medical

records. Unless evidence is obtained for existence of allergies, no testing is recommended. Random selection is required among subjects having values for any parameters found to deviate from normal ranges.

Standardized neurological exams and phychological tests are frequently employed to document the presence of attentional deficits, distractability, poor coordination, soft neurological signs, and so forth.

If a non-hyperactive learning disability subgroup is to be included, it is considered desirable to require at least one year of retardation in reading and/or arithmetic on a standard test of achievement such as the Peabody Achievement Test.

Characterization of the study sample with regard to possible etiology as well as with regard to parameters of CNS functioning such as level of cortical arousal may also be desirable because of the heterogeneity of the group of children who are characterized as hyperactive, MBD, learning disorders, etc.

The sample should also be characterized with regard to social class, family integration, and other types of previous therapy, such as pharmacotherapy, family counseling, tutoring, special education, and behavior modification. Detailed information

should be collected on eating habits and a careful dietary history should be taken on all children. These data might provide new important predictor information for understanding the subgroup of children who evidence maximal therapeutic improvement. Thus, for example, by regressing scores representing the adequacy of the child's eating habits and prior nutritional intake against improvement in symptomatology (associated with the K-P diet and/or the control diet), it becomes possible to determine the extent to which prior dietary adequacy may modify the the magnitude of the therapeutic response to the dietary intervention. If general nutritional factors played an etiological role in hyperkinesis, one would expect reliably more improvement in those children who initially had histories of poor eating habits and nutritionally impoverished diets.

7) Adequate Baseline Observations. Since many rating instruments are characterized by "practice" effects and since many hyperkinetic children are on treatment regimens which may have to be terminated in order to make them eligible for dietary study protocols, it is very important that adequate baseline periods be employed to allow for pretreatment stability of target symptoms.

8) Dietary Specification and Evaluation with Regard to: a) general nutritional adequacy: b) compliance with dietary specifications

in terms of both inclusions and exclusions. It should be realized that to the extent that children deviate from the K-P diet (which contains no artificial food colors or food flavors) the likelihood of finding support for the efficacy of the K-P diet is diminished. For this reason, an inpatient setting which would provide the opportunity for very close supervision of food intake would seem desirable. When obvious dietary violations occur, whether in an inpatient or outpatient trial, the data from that patient (whether on the control or K-P diet) should be excluded from all data analyses. Whatever the diet the child is given, K-P or "control," actual food intake should be carefully specified and closely monitored.

For an individual child, 5- or 7-day records are considered adequate for determining intakes of the major nutrients such as carbohydrate or protein. Twenty-four hour recalls are considered inadequate to assess nutrient intakes of groups of children. The number of children needed to obtain valid information from 24-hour recalls, under a variety of circumstances, has never been very well defined. Because of the variability of intake of trace nutrients, food additives, or contaminants and the requirement for accurate and precise knowledge of intake, it is recommended that three continuous weeks of records of food intake be obtained for each child.

Analysis of foods should include iron, zinc, lead, and color additives, if possible. Estimation of dietary fat, protein, carbohydrates, tyrosine, and tryptophan shall be calculated from dietary intake using table values.

In order to maximize the likelihood of dietary compliance, the entire family should follow the diet prescribed for the child. Further, it would seem prudent for the research team to provide the food for the complete diet to the entire family for the full duration of the clinical trial.

The control diet should provide levels of all nutrients equal to those established by the Recommended Dietary Allowances of the National Academy of Sciences.

The National Advisory Committee on Hyperkinesis and Food Additives in their report to the Nutrition Foundation (June 1, 1975) were so concerned with a true double-blind testing of the K-P diet that they state, " ... in a home setting there be used but one diet, i.e., no "control diets," because of anticipated difficulty in assuring compliance and the impossibility of avoiding the placebo effect."

They indicate further, "... the utilization of alternative dietary plans, i.e., the K-P diet and a "control," even when randomly administered, precludes strict double-blind testing

and introduces the variable placebo effect."

9) Multiple Outcome Criteria. Whenever possible, it is suggested that a variety of raters and a variety of different types of outcome criteria be included to evaluate therapeutic response. Thus, types of raters might include (a) parents; (b) teachers; (c) school peers; (d) clinicians; and (e) trained observers independent of the study per se. Elements of rating might include: (a) attentional tasks; (b) learning tasks (such as paired-associate learning, recognition, mazes, etc.); (c) objective measures of activity such as actometers, stabilimetric cushions, grid crossing, etc; (d) subjective estimates of behavioral change in activity level, distractability, impulsivity, ability to sustain attention, sociability, and so on, by the different types of raters indicated above.

10) Study Duration. Most treatment regimens for the hyperkinetic child syndrome are administered over extended periods of time, e.g., years. While typically the initial treatment efficacy of a particular regimen is established in the context of a short-term treatment protocol, e.g., a few months, it ultimately becomes most important to encourage and support the collection of long-term efficacy and safety data. The early recognition and public health commitment to this stratagem is particularly important when dealing with the still developing child. The possibility of late onset of adverse effects, stemming from a treatment with an established short-term efficacy and safety record, must not be overlooked. Naturally, this consideration

only becomes of concern if short-term efficacy and safety are firmly established. The prudent investigator should consider the necessary logistics for the long-term followup of study cohorts and should plan for a six-month or twelve-month followup to obtain some information with regard to whether or not the prescribed study diet is still being followed and how the child is doing at home and at school.

11) Sample Size. The sample size necessary to demonstrate a statistically significant difference between two relevant regimens depends upon the "true" magnitude of treatment differences and upon the magnitude of sources contributing to subject variability and errors of measurement. Preliminary projections based upon pilot data suggest that a study population of between 30 and 60 should be required to be fairly certain of detecting a 20 percent difference in response between the K-P regimen and a control regimen. The above projection is based on a crossover design and roughly twice this sample size (70-100 children) would be required to obtain this sama degree of sensitivity in an independent group design.

MODEL DESIGNS

Model Design A

To determine whether there is any therapeutic benefit to be derived from any aspect of the Feingold dietary regimen (general nutritional component + psychosocial changes in the family interactions + specific elimination of artifical food colors and food flavors), one

might identify a suitable group of children diagnosed as having the hyperkinetic reaction of childhood and randomly assign half the sample to a treatment waiting list (for ethical reasons only a few weeks should be used) while the other half of the sample received the Feingold diet. Pre- and post-treatment evaluations on an appropriate battery of therapeutic outcome measures and tests would provide an overall evaluation of the Feingold regimen. Some information regarding the importance of the general nutritional component of the Feingold regimen might be obtained by taking a careful dietary history of all children assigned to the study and examining the magnitude of therapeutic improvement on the Feingold regimen against the prior nutritional adequacy of the child's diet. If those children who were judged initially to have the least adequate diets evidenced the most improvement on the Feingold regimen, this relationship would be suggestive of a general therapeutic benefit from the non-specific nutritional component of the K-P diet.

Issues of dietary compliance are of considerable importance in evaluating the results of data generated from studies employing this type of design.

Since it is rather generally accepted that any dramatic psychosocial and/or quasi-medical intervention is likely to result in at least some therapeutic benefit, this Model Design A does not seem particularly relevant except insofar as it may cast some light on issues related to a possible association between nutrition and

behavior.

Model Design B

The Blue Ribbon Panel (see appendix) made the point that hyperkinesis may be associated with hunger and it seems clear that behavioral disorders may also be associated with nutritional deficiencies of various kinds.

In order to determine the general nutritional benefit of various diets, including the Feingold regimen, it must be possible to develop an appropriately large sample of children with the hyperkinetic syndrome and randomly assign them to either the K-P diet or another diet, judged by a group of nutritional experts to be nutritionally adequate. In order to equalize "placebo effects" the control diet should involve the same degree of dietary difficulty for preparation as the K-P diet. This design might proceed as an independent group design (no crossover) or as a counter-balanced crossover design in which the sequence of diets was randomized.

Issues with regard to dietary compliance and with regard to the double-blind condition of the study will require careful monitoring. In this regard it would be helpful for potential investigators in this area to develop standardized procedures and questionnaires to tap these important concerns prior to the initiation of studies with this type of design because of the difficulty in maintaining the double-blind.

It must be stressed that Model Design B provides information with regard to general dietary response and not with regard to specific dietary additives per se.

Model Design B is not as straightforward as Model Design C (vide infra) and is open to more possible sources of bias with regard to the potential breaking of the double-blind and issues around dietary compliance. It does address the broader public health concern of general nutritional factors and their possible etiological significance for the symptoms of the hyperactive child syndrome. It also provides some opportunity to examine the more specific Feingold hypothesis but in a less direct fashion than does Model Design C.

It must be recognized that "diet" represents a most complex independent variable in that two diets may differ along many nutritional dimensions so that finding a therapeutic advantage (or disadvantage) for the K-P diet vs. the control diet would not enable the researcher to conclude that the differences between the diets was necessarily attributable to the presence or absence of artificial food colors and food flavors.

Model Design C

The most direct test of the Feingold hypothesis is one in which the children who have responded to his diet be maintained on the same treatment regimen plus the addition, in a double-blind fashion, of chocolate cookies, candy, or other food items prepared in such a fashion that one-half of the items will contain no food additives and the other half will contain the eight more common food additives at levels calculated to average what a child on an

ordinary diet might take in daily.

The selection of challenge components and/or factors should be prioritized according to the distribution and relative concentration of suspect materials in the food supply. Consideration should also be given to the scientific evidence that might support the selection of particular compounds.

Levels of challenge materials to be used in the diet shall be established by estimating the levels normally found in foods. The use of quantities above the levels normally found in food should only be sanctioned where safety is assured and where additional amounts will provide some beneficial effect.

Given this general model one could use either an (a) "independent" group design (if the sample size was sufficiently large) with children randomly assigned to the "pure" K-P diet or the K-P "challenge" diet; (b) a counterbalanced crossover design in which each child serves as his own control and is randomly assigned to either the "pure" to "challenge" sequence or the "challenge" to "pure" sequence (fewer children would be needed to achieve the same degree of statistical power as compared with the "independent" group designs); or (c) a multiple crossover design such as proposed by Dr. Chassan (see Principals and Problems in Establishing the Efficacy of Psychotropic Agents; (Eds.) Levine, Schiele, and Bouthilet, 1971) and has come to be called the "intensive" design. It should be noted that the "intensive" design provides for sufficient crossover data points to permit the statistical evaluation of dietary effects for each child included in the study. All

variants of the Model Design "C" permit a direct test of the specific Feingold hypothesis that artificial food flavors and colors (or whatever constituents are put into the challenge chocolate bar) are directly associated with adverse behavioral effects, such as hyperactivity, poor attention span, distractability, irritability, etc.

This type of design does not provide a general test of the K-P regimen insofar as that regimen may be nutritionally superior to the child's previous nutritional intake or insofar as the K-P regimen is likely to provide the child with a generally more therapeutic type of interaction with other members of the family. Should the results of this type of study design prove positive: i.e., children receiving the food color-flavor additives show statistically significant deleterious effects relative to the pure K-P dietary condition, then by the process of eliminating different constituents of the challenge, it would be possible to pinpoint the particular dietary offenders either on a group basis or on an individual basis, if an intensive design was employed.

The possible mechanisms of action might also be explored if it was finally established that the Feingold hypothesis was indeed correct. Should the results of studies conducted with Model Design "C" prove negative, one might then make a decision with regard to the public health significance of evaluating the other aspects (general nutritional components and psychosocial components) of the Feingold regimen. From a scientific perspective, this design is

clearly superior to other possible designs in terms of preserving the double-blind. The preservation of the double-blind is, of course, most critical to the subjective interpretations of therapeutic change made by parents, teachers, and members of the treatment team.

Since Dr. Feingold has claimed that only from 30 percent to 50 percent of hyperkinetic children show improvement on the K-P diet, the ICGH strongly recommends that children be pretested on the K-P diet in an open pre-study phase and that only those children who show a "good" response to the K-P regimen be entered into the more formal (i.e., double-blind) study design. It was also suggested that washout periods be inserted between the K-P diet and the K-P challenge diet (to control for possible pharmacologic carryover effects) and that an A-B-A vs B-A-B sequence be employed to avoid the potential statistical problems in an A-B vs B-A crossover design in which a sequence by treatment interaction can cloud the interpretation of pooled treatment differences.

Model B and C Combined

One interesting variant of the designs discussed above is the possibility of combining aspects of Model Design B with Model Design C. Thus, for example, one could start with a pool of carefully diagnosed hyperkinetic children who were randomly assigned to either the K-P diet or a nutritionally adequate control diet which contained artificial food colors and food flavors (Model Design C). After an appropriate dietary trial of four weeks on each diet, using a cross-over design, those children showing a favorable therapeutic response to the K-P diet but not to the control diet would enter a Model Design C Study, i.e., K-P vs. K-P challenge in a counter-balanced, double-blind, crossover sequence.

The initial phase of this study would provide information about dietary response (Model Design B) whereas the second phase of the design (Model Design C) would provide more specific information about the role of food colors and food flavors. One advantage for this combination Design is that it would cast light on both the percentage of hyperkinetic children who were responsive to general dietary regimens as well as to the more specific aspects of the K-P dietary regimen.

SUMMARY

The Interagency Collaborative Group on Hyperkinesis has held five formal meetings and numerous informal meetings over the past three

months in order to carry out its assignment.

One of these meetings consisted of an all day conference on hyperkinesis and diet attended by scientists from several universities and representatives from the legal profession, press and consumer groups. The Group has directed its efforts toward an exchange of information concerning some of the research issues relevant to hyperkinesis and diet, a review of the appropriate literature, assessment of ongoing or completed research studies, and a review of several proposed studies in order to explore whether or not dietary modification contributes significantly to a reduction of symptoms in children with the hyperkinetic syndrome.

The clinical definition of the hyperkinetic syndrome typically excludes children of less than low normal intelligence. The major symptoms of the hyperkinetic syndrome are an increase of purposeless physical activity and a significantly impaired span of focused attention. The child is easily distracted, racing from one idea or interest to another.

The diagnosis is clearly best made by a skilled observer and, unfortunately, there is no single diagnostic test. As a result of diagnostic difficulties, crude estimates of the prevalence of the hyperkinetic syndrome vary considerably. One conservative estimate is that 3 out of 100 elementary school children have moderate to severe behavioral disorders. However, a five-fold range in estimates of prevalence made it impossible to determine the true

number of children showing behavior patterns associated with hyperkinesis.

Although many factors seemed to be involved in the etiology of the hyperkinetic behavioral syndrome, specific factors have been implicated in some individual cases.

The Group reviewed some of the observed relationships between the occurrence of the hyperkinetic syndrome in children and such factors as the social environment, biochemical, nutritional status, allergy or intolerance to foods and exposure to toxic substances.

SOCIAL FACTORS:

It would be difficult to over-emphasize the importance of the social environment in discussing the etiology of behavior syndromes in children. Tensions arising from poor social relationships can trigger hyperactive behavior which may contribute to further deterioration of relationships between the child and his parents, teachers and peers. However, caution must be exercised in employing simple explanations of the effects of increased activity on socialization. It has been proposed that moderate to high levels of activity usually go along with social success. Even though a social-behavioral view of hyperkinetic behavior is undoubtedly incomplete, some awareness of social factors is necessary in considering etiology and in making treatment plans for the hyperkinetic child.

NUTRITIONAL STATUS:

One of the ways diet may have effects on behavior is by modifying the biochemistry of the nervous system. Alterations in the quality, quantity, and timing of intake of food ingredients can involve changes which may affect the body's metabolism and the function of various organs, including the brain. Deficiencies of nutritionally required ingredients such as vitamins are one potentially relevant mechanism.

Some cases of the hyperkinetic syndrome have been linked etiologically to hypoglycemia (low glucose availability). In such individuals who are susceptible to reactive (post absorptive) hypoglycemia, the relative proportions of energy yielding nutrients available to the central nervous system can affect the occurrence of symptoms.

ALLERGY, INTOLERANCE, AND TOXICITY:

It has recently been suggested that the occurrence of hyperkinesis and learning disabilities in children, and of sleeplessness, irritability and colic in infants, is linked to the ingestion of artificial food colors and flavors in foods. A diet free of these food additives has been advocated by some individuals as a means of reducing the symptom level of children with the hyperkinetic-behavior syndrome. A limited number of research studies have attempted to verify this hypothesis.

CONCLUSIONS:

The Group has reviewed the available data and information from those dietary studies which have been completed and made available for review. All of these studies have methodological problems consisting of small study populations, difficulties in maintaining a "blind" component in the use of diet, difficulty in imposing dietary restrictions and questions concerning data analysis.

Only when the children, parents, and evaluators of behavioral changes are unaware of which diet is being ingested by the children studied can biases based on hope and expectations of improvement in behavior be avoided.

It is the opinion of the Group that these studies have neither proven nor disproven the hypothesis that a diet free of artificial food colors and flavors reduces the symptoms in a significant number of children with the hyperkinetic-behavior syndrome. The Group feels, however, that the evidence taken as a whole is sufficient to merit further investigation into the relationship of diet and the hyperkinetic syndrome.

RECOMMENDATIONS:

The Group urges that basic behavioral, neurophysiological, and biochemical research in the area of hyperkinesis receive continued support. The possibility that fundamental neurochemical abnormalities underlie many of the manifestations of hyperkinetic behavior is a real

one, and the research efforts needed to find these answers are broader than just those discussed in this report.

The Group recognizes that a valid assessment of the Feingold dietary regimen must be designed to test the general therapeutic change that may follow from a mixture of the three components of the regimen, i.e., general nutritional changes, altered social interactions and the elimination of artificial food flavors and colors with the separation and assessment of these components to be carried on in an age-continuum of infants, and 1-5 and 6-12 year old children.

The Group is aware that one study presently underway will be completed as of early December and the data analyzed for presentation and review by early 1976. The Group believes that further study with these children should be performed if feasible. Such a study (Model C) would involve testing the children responsive to the K-P diet with food preparations having quantities of artificial food colors and/or flavors consistent with average dietary intakes.

The Group also believes it important to perform another efficacy study of the dietary regimen in an outpatient population (Model B), to be followed by a challenge (Model C) type study on the same population's responders to the K-P diet.

Of additional current importance would be a study to explore whether or not infants with colic, or young children who show high levels of irritability, fidgetiness, sleeplessness and crying, exhibit such behavioral characteristics as a result of intolerance to artifical food colors and/or flavors.

If the studies above demonstrate positive results supporting the efficacy of the K-P dietary regimen in reducing the symptoms of children with the hyperkinesis syndrome, it then becomes a more complex problem to define the etiologic factors and mechanisms involved.

APPENDIX A

REPORT

OF THE CONFERENCE ON THE USE OF STIMULANT DRUGS IN THE TREATMENT OF BEHAVIORALLY DISTURBED YOUNG SCHOOL CHILDREN

Sponsored by the Office of Child Development and
the Office of the Assistant Secretary for Health and Scientific Affairs
Department of Health, Education and Welfare
Washington, D.C., January 11-12, 1971

CONTENTS

Introduction..... 1

Behavior Disorders of Childhood..... 2

"Hyperkinetic Disorders"..... 3

Incidence of Hyperkinetic Disorders..... 3

Causes of Hyeprkinetic Disorders..... 4

The Course of Hyperkinetic Disorders..... 4

Diagnosis of Hyperkinetic Disorders..... 5

Treatment Programs..... 6

Concerns Raised by the Public and the News Media..... 8

1. Does the medication produce toxicity?..... 9

2. Is there a risk of drug dependency in later years?..... 9

3. Are there safeguards against misuse?.....10

4. Do stimulants for children create a risk for others?.....10

5. Does medicction handicap the child emotionally?.....11

6. What are the rights of the parents?.....12

Stigmatizing the Medicines and Children, and the Role of Public Education.....12

The Promotion of drugs by Industry and the Media.....13

The Delivery of Special Health Care: A Dilemma.....14

The Needs for Skills and Knowledge.....14

Participants in the Panel.....17

Introduction

On January 11-12, 1971, the Office of Child Development and the Office of the Assistant Secretary for Health and Scientific Affairs, Department of Health, Education, and Welfare, called a conference to discuss the use of stimulant medications in the treatment of elementary school-age children with certain behavioral disturbances. In convening the conference, the Office of Child Development was aware of public concern about the increasing use of stimulant medications (such as dextroamphetamine and methylphenidate) in treating so-called hyperkinetic behavior disorders. Were these drugs--so widely misused or abused by adolescents and adults--truly safe for children? Were they properly prescribed, or were they used for youngsters who, in fact, need other types of treatment? Is emphasis on medications for behavior disorders misleading? Might this approach tempt many to oversimplify a complex problem, leading to neglect of remedial social, educational or psychological efforts on the part of professionals, parents, schools and public agencies?

In order to clarify the conditions in which these medications are beneficial or harmful to children, to assess the status of current knowledge, and to determine the best auspices for administering these drugs to children, a panel of fifteen specialists was invited to meet in Washington. The panelists were from the fields of education, psychology, special education, pediatrics, adult and child psychiatry, psychoanalysis, basic and clinical pharmacology, internal medicine, drug abuse and social work. The panel's task was to review the evidence of research and experience and to prepare an advisory report for professionals and the public.

This report briefly outlines the general nature of behavioral disorders in children and then focuses on those disorders that are being treated with stimulant medications. It discusses appropriate treatment and the concerns voiced by the public and media. Finally, the report examines the role of the pharmaceutical industry, professionals, and the news media in publicizing stimulant drugs for children and outlines the glaring gaps in needed research, training and facilities.

Behavior Disorders of Childhood

A wide range of conditions and disabilities can interfere with a child's learning at home and in school, his socialization with peers, and his capacity to reach his maximum development. Social deprivations and stress at home or school may retard optimal development. Mental retardation, the more rarely occurring childhood autism and psychosis, and other such disabilities may cause serious problems. Some difficulties arise because of clearly definable medical conditions such as blindness, deafness or obvious brain dysfunction. Some are associated with specific reading or perceptual defects, and others with severe personality or emotional disturbance.

Such dysfunctions are known to require careful evaluation, thoughtfully planned treatment employing a variety of methods on the child's behalf, and conscientious monitoring of remedial treatments. Individualized evaluation and treatment is important for any childhood behavior disorder. There are appropriate occasions for use of medications such as tranquilizers and anti-depressants in some children with these disorders. For over three decades, stimulant medications have been selectively used for children under medical supervision. We now focus upon issues related to the current use of these drugs.

"Hyperkinetic Disorders"

The type of disturbance which has evoked misunderstanding and concern has many names. The two most familiar--neither entirely satisfactory--are "minimal brain dysfunction" or, more commonly, "hyperkinetic behavioral disturbance." There is no known single cause or simple answer for such problems. The major symptoms are an increase of purposeless physical activity and a significantly impaired span of focused attention. The inability to control physical motion and attention may generate other consequences, such as disturbed mood and behavior within the home, at play with peers, and in the schoolroom.

In its clear-cut form, the overt hyperactivity is not simply a matter of degree but of quality. The physical activity appears driven--as if there were an "inner tornado"--so that the activity is beyond the child's control, as compared to other children. The child is distracted, racing from one idea and interest to another, but unable to focus attention.

Incidence of Hyperkinetic Disorders

This syndrome is found in children of all socioeconomic groups and in countries throughout the world. A conservative estimate would be that moderate and severe disorders are found in about 3 out of 100 elementary school children--an estimate that would vary somewhat in different communities. More males than females are affected, as is true in a number of childhood ailments. Children so afflicted are generally of normal or superior intelligence. A significant number so diagnosed have special learning or reading disabilities, in addition to the major sypmtoms. A near majority are reported to have had behavioral problems since infancy. There is a smaller group of more severely afflicted

children upon whom most studies have focused; they may show increased clumsiness and a variety of physical symptoms. Thus, some of the children show hyperactivity and reduced attention which ranges in degree from mild to severe, with or without associated physical signs or special learning impairments; some have complex behavioral and personality problems, as well as special learning and reading difficulties, along with the major hyperkinetic symptoms.

Causes of Hyperkinetic Disorders

We know little about definitive causes. The disorder has been ascribed to biological, psychological, social or environmental factors, or a combination of these. There is speculation that the core set of symptoms--those affecting control of attention and motor activity--may have their origin in events taking place before the child is born, or during the birth process, or they may be related to some infection or injury in early life. The neurological and psychological control of attention is an important but incompletely researched topic, as are the nutritional, perinatal and developmental factors. Thus, in many instances, it is not yet possible even to speculate as to original causes.

The Course of Hyperkinetic Disorders

Usually, the excessive activity and attentional disturbances are less apparent after puberty. Specialists citing experience and some fragmentary research data believe that treatment enables many to lead productive lives as adults, while severely afflicted children who remain untreated may be significantly at risk for adult disorders. Extensive research is still required on these points. Because the ages of 5 to 12 are crucial to the child's

development and self-image, treatments which permit the child to be more accessible to environmental resources are warranted and useful.

Diagnosis of Hyperkinetic Disorders

In diagnosing hyperkinetic behavioral disturbance, it is important to note that similar behavioral symptoms may be due to other illnesses or to relatively simple causes. Essentially healthy children may have difficulty maintaining attention and motor control because of a period of stress in school or at home. It is important to recognize the child whose inattention and restlessness may be caused by hunger, poor teaching, overcrowded classrooms, or lack of understanding by teachers or parents. Frustrated adults reacting to a child who does not meet their standards can exaggerate the significance of occasional inattention or restlessness. Above all, the normal ebullience of childhood should not be confused with the very special problems of the child with hyperkinetic behavioral disorders.

The diagnosis is clearly best made by a skilled observer. There unfortunately is no single diagnostic test. Accordingly, the specialist must comprehensively evaluate the child and assess the significance of a variety of symptoms. He considers causal and contributory factors--both permanent and temporary--such as environmental stress. He distinguishes special dysfunctions such as certain epilepsies, schizophrenia, depression or anxiety, mental retardation or perceptual deficiencies. The less severe and dramatic forms of hyperkinetic disorders also require careful evaluation. Adequate diagnosis may require the use not only of medical, but of special psychological, educational and social resources.

Treatment Programs

The fact that these dysfunctions range from mild to severe and have ill-understood causes and outcomes should not obscure the necessity for skilled and special interventions. The majority of the better known diseases--from cancer and diabetes to hypertension--similarly have unknown or multiple causes and consequences. Their early manifestations are often not readily recognizable. Yet useful treatment programs have been developed to alleviate these conditions. Uncertainty as to cause has not prevented tests of the effectiveness of available treatments, while the search for clearer definitions and more effective kinds of therapy continues. The same principles should clearly apply to the hyperkinetic behavior disorders.

Several approaches now appear to be helpful. Special classes and teachers can be directed to specific learning disabilities and thus restore the confidence of the child who experiences chronic failure. Modification of behavior by systematic rewarding of desired actions has been reported to be useful in some children. Elimination of disturbing influences in the family or classroom through counseling may often tip the balance, and a happier child may show improved control and function.

There will be children for who such efforts are not sufficient. Their history and their examination reveal symptoms of such a driven nature that skilled clinicians undertake a trial of medical treatment. Medicine does not "cure" the condition, but the child may become more accessible to educational and counseling efforts. Over the short term and at a critical age, this can provide the help needed for the child's development.

Stimulant medications are beneficial in only about one-half to two-thirds of the cases in which trials of the drugs are warranted. The stimulant drugs

are considered to be the first and least complicated of the medicines to be tried. Other medications--the so-called tranquilizers and anti-depressants--are generally reserved for a smaller group of patients. Without specialized medical therapy, the consequences for these children of their failure to manage--even in an optimal environment--are clearly very severe. In such cases, the aim is not to "solve problems with drugs," but to put the severely handicapped child in a position to interact with his environment to the extent that his condition permits.

Response to stimulant medication cannot be predicted in advance. Fortunately, the issue can be resolved quickly. When stimulants are given in adequate doses, a favorable response--when it occurs--is fairly rapidly obtained and is unmistakably the consequence of the drug. Thus, if an adequate test of pharmacotherapy (a few days or weeks) produces only doubtful benefits or none at all, treatment can be promptly terminated. The physician will, of course adjust dosage carefully to assure an adequate therapeutic trial. It would be tragic to deprive a child of a potentially beneficial treatment by inattention to dose. Thus, it is clear that not all affected children require medication and that of those who do, not all respond.

When the medication is effective, the child can modulate and organize his activities in the direction he wishes. The stimulant does not slow down or suppress the hyperkinetic child in the exercise of his initiative. Nor does it "pep him up," make him feel high, overstimulated, or out of touch with his environment. Much has been made of the "paradoxical sedative" effect of stimulants in such children. The term is inappropriate. Although their exact mechanism of action is not known, stimulants do not provide a chemical straitjacket. They do not act as a sedative. Rather, they appear to mobilize and

to increase the child's abilities to focus on meaningful stimuli and to organize his bodily movements more purposefully.

The hoped-for secondary consequences are better peer relationships, improved self-image, and pleasure in acquiring competencies. Any coexisting dysfunctions--such as special perceptual and learning handicaps--must not be left unattended, simply because pharmacotherapy is available and sometimes helpful. Similarly, personality and psychological problems, social and family problems, may require continued attention.

During drug treatment, the dosage may require shifting to minimize unwanted effects, of which the major ones are loss of appetite and insomnia. Drug treatment should not and need not be indefinite, and usually is stopped after the age of 11 or 12. Frequently, following a sustained improvement over several months or a year or so, drugs may be discontinued, as during a vacation period. Drug-free intervals can be prolonged as observers assess the child's condition.

The decision to use drug treatment thus depends on the commitment to diagnose and to monitor the response to treatment in the best traditions of medical practice. When there is informed parental consent, parents, teachers and professionals can collaborate in organizing and monitoring treatment programs.

Concerns Raised by the Public and the News Media

We will now turn to various concerns about hazards and abuses when stimulant medications are used for children. For example, concern has been expressed that the medical use of stimulants could create drug dependence in later years or induce toxicity. This subject touches on the rights of the child to needed treatment, as well as risks to both the child and the public, and requires continued intensive scrutiny.

1. Does the medication produce toxicity?

One should not confuse the effects of intravenous stimulants and the high dosages used by drug abusers with the effects or the risks of the low dosages used in medical therapy. In the dosage used for children, the questions of acute or chronic toxicity noted in the stimulant abuser are simply not a critical issue. Unwanted mental or physical effects do rarely appear in children; cessation of therapy or adjustment of dosage quite readily solves the problem.

2. Is there a risk of drug dependency in later years?

Thirty years of clinical experience and several scientific studies have failed to reveal an association between the medical use of stimulants in the pre-adolescent child and later drug abuse. Physicians who care for children treated with stimulants have noted that the children do not experience the pleasurable, subjective effects that would encourage misuse. They observe that most often the child is willing to stop the therapy, which he views as "medicine." Thus, the young child's experience of drug effects under medical management does not seem to induce misuse. The medical supervision may "train" him in the appropriate use of medicines. When adults are given stimulants--or even opiates--for time-limited periods under appropriate supervision and for justifiable reasons, there is relatively little misuse. Similarly, in treating epilepsy, barbiturates have been given from infancy to adulthood without creating problems of dependency or abuse.

It is not ordinarly the drug which constitutes abuse but the way in which a drug and its effects are used and exploited by an individual. There are indeed adolescents who; in varying degrees and for varying periods of time either misuse or dangerously abuse stimulants. They experiment with the effects of

excessive dosages to create excitement, to avoid sleep, to defy contraints, and to combat fatigue and gloom. It should be noted that these drugs are not commonly prescribed to children after the age of 11 or 12, when the actual risks of such experimentation or misuse might possibly become more significant.

Alert monitoring of drug use at any age is a part of sensible medical practice. With such precaution and with the available evidence, we find minimal cause for concern that treatment will induce dangerous drug misuse. To the contrary, there are very good reasons to expect that help, rather than harm, will be the result of appropriate treatment.

3. Are there safeguards against misuse?

There are some sensible steps, in addition to medical control, that guard against possible misuse. The child should not be given sole responsibility for taking the medication. He usually need not bring the drug to school. The precautions that surround the medicine cabinet--whether antibiotics, aspirins, sedatives or other medications are present--should be applied. Many such medicines, when misused, can be more dangerous to health and life than even the stimulant drugs. No child in the family should have access to medications not presecribed for him. These are general precautions comprising a part of the child's eduction in the "etiquette of the medicine cabinet."

4. Do stimulants for children create a risk for others?

The panel agrees that stimulant drug abuse is seriously undesirable and frequently dangerous, although views vary on the scope of the problem and the number of actual casualties. Experts also agree that far more stimulants are prescribed for adults than are medically needed and far more are manufactured than prescribed.

Overprescription of any medication is deplored, whether or not it is liable to abuse. The question is whether the availability of stimulants for a very few of the childhood behavior disorders threatens the public health.

The prescribed dosage for an individual child constitutes an insufficient quantity to supply the confirmed abuser of stimulants with the amounts he requires. It is also true that illicitly manufactured stimulants are quite readily available and abused in this country. We must weigh the advantages of having appropriate medication available against the dangers of withholding treatment from a child who can clearly benefit from it. We doubt that prescriptions for the children who benefit from stimulants will require the manufacture of excessive and dangerously divertible supplies. With sensible precautions, there is at present no evidence justifying sensational alarm. either about the safety of the individual child who can benefit from therapy or about the safety of the general public.

5. Does medication handicap the child emotionally?

It is sometimes suggested that treated children may not be able to learn normal responses and master adjustments to the stresses of everyday life. These fears are understandable but are not confirmed by specialists who have experience with the conditions and the situations in which medications are properly used. For the correctly diagnosed child, these medications--if they work at all--facilitate the development of the ability to focus attention and to make judgments in directing behavior. Such children can acquire the capacity to tolerate the master stress. The medications, in these circumstances, help "set the stage" for sstisfactory psychological development.

The hyperkinetic behavioral disturbance is a form of diorganization that creats great stress in the afflicted child. The use of therapeutic

stimulants for this disturbance should not be equated with the misuse of medication aimed at allowing a normal child or adult to avoid or escape the ordinary stresses of life.

6. What are the rights of the parents?

Under no circumstances should any attempt be made to coerce parents to accept any particular treatment. As with any illness, the child's confidence must be respected. The consent of the patient and his parents or guardian must be obtained for treatment. It is proper for school personnel to inform parents of a child's behavior problems, but members of the school staff should not directly diagnose the hyperkinetic disturbance or prescribe treatment. The school should initiate contact with a physician only with the parents' consent. When the parents do give their approval, cooperation by teachers, social workers, special education and medical personnel can provide valuable help in treating the child's problem.

Stigmatizing the Medicines and Children, and the Role of Public Education

A child who benefits from stimulants or other psychotropic medications should not be stigmatized; his situation is no different from that of the child who benefits from eyeglasses. It is unjust to stigmatize a child in later life, when competing in various situations (applying for college, employment or organization memberships), by labeling him early in life as "stupid" an "emotional cripple," a "drug-taker," or by any other kind of unjustified and unfortunate stereotype.

Nor should the medicine be stigmatized. Where bad practices prevail--and a number of complaints have been called to our attention--these practices should be squarely dealt with. This is not only a responsibility of physicians and educators, but also of the news media. Yet indignation must be tempered with perspective and scrupulous respect for the facts. An informed and understanding public can foster the growth and development of children, and these public attitudes may lead to the development of more refined and better-delivered health services. Either bad practices or exaggerated alarm can threaten the availability of medical resources for those who critically need it. This has happened before in the history of valuable medicines and it can take years to repair the damage.

The Promotion of Drugs by Industry and the Media

Pharmaceutical companies producing stimulants or new medications which may become useful for hyperkinetic disorders have a serious obligation to the public. These medicines should be promoted ethically and only through medical channels. Manufacturers should not seek endorsement of their products by school personnel. In the current climate, society can best be served if industry refrains from any implicit urging that nonspecialists deal with disorders and medications with which they are unfamiliar. Professionls and the news media can play useful roles by not pressing for treatments in advance of their practical availability.

The Delivery of Special Health Care: A Dilemma

Our society has not as yet found complete solutions to the problem of the delivery of special health care. When available treatments cannot be confidently and appropriately delivered by physicians, they are perhaps best withheld until such treatments can be provided--especially with milder dysfunctions. This is not to say that severly afflicted hyperkinetic children should not or cannot receive available medical treatment. But until systems of continuing professional education and ready access to consultants are financed and perfected, some judgment about the pace at which unfamiliar treatments can be widely fostered is required. Finally, we must recognize that it is not only the scarcity of trained personnel, but factors such as poverty and inadequate education facilities which prevent accessibility to individualized treatment.

The Need for Skills and Knowledge

In preparing this report, the Committee was repeatedly struck by our lack of information in many crucial areas. The facts are that children constitute well over half our population, but receive a disproportionately low share of skilled research attention. We have noted the difficulties in arriving at accurate methods of diagnosis and the importance of launching careful longitudinal and follow-up studies. The investigation of causal factors lags. Such factors as perinatal injury, environmental stress or the development of the neurological and psychological controls of attention require study. Variations

in different socioeconomic and ethnic groups must be considered in order to arrive at better definitions of behavior properly regarded as pathological. All such research efforts would have aided us in assessing the numbers of affected children and in recommending designs for more effective treatment programs.

Clinical pharmacologists have repeatedly found that drugs may act differently in children than in adults. To use medicine of all kinds effectively in children, more specialists must be trained in drug investigation--pharmacologists who can develop basic knowledge about the action of drugs in the developing organism. There is the obvious need for better and more precisely targeted drugs for the whole range of severe childhood behavior disorders. This requires intense research and training efforts. Such efforts provide the means for developing, testing and delivering better treatment programs. There is a similar need for research in the techniques of special education and also a need to make these techniques available to children who can benefit. It would appear to be a sound Federal investment to conduct such research and training.

In summary, there is a place for stimulant medications in the treatment of the hyperkinetic behavioral disturbance, but these medications are not the only form of effective treatment. We recommend a code of ethical practices in the promotion of medicines, and candor, meticulous care and restraint on the [illegible] of the media, professionals and the public. Expanded programs of continuing education for those concerned with the health care of the young, and also sustained research into their problems, are urgently needed.

Our society is facing a crisis in its competence and willingness to develop and eliver authentic knowledge about complex problems. Without such knowledge, the public annot be protected against half-truths and sensationalism, nor can the public advance its concern for the health of children.

PARTICIPANTS IN THE PANEL

Dr. Daniel X. Freedman, Chairman
Professor and Chairman, Department of Psychiatry, University of Chicago

Dr. T. Berry Brazelton
Practicing pediatrician and Research Associate and Lecturer in Cognitive Studies, Harvard University

Dr. James Comer
Associate Professor of Psychiatry, Yale Study Center, and Associate Dean, Yale Medical School

Dr. William Cruickshank
Director, Institute for the Study of Mental Retardation, University of Michigan

Dr. Edward Perry Crump
Professor of Pediatrics, Meharry Medical College. Nashville, Tennessee

Dr. Barbara Fish
Professor of Child Psychiatry, New York University School of Medicine

Dr. George H. Garrison
Clinical Professor of Pedicatrics, University of Oklahoma

Dr. Frank Hewett
Associate Professor in Special Education and Psychiatry, University of California

Dr. Leo E. Hollister
Clinical pharmacologist and Medical Investigator, Veterans Administration Hospital, Palo Alto, California

Dr. Conan Kornetsky
Research Professor, Division of Psychiatry and Department of Pharmacology, Boston University School of Medicine

Dr. Edward T. Ladd
Professor of Education, Emory University, Atlanta, Georgia

Dr. Robert J. Levine
Associate Professor of Medicine and Pharmacology, Yale University School of Medicine

Dr. Patricia Morisey
Associate Professor, School of Social Service, Fordham University

Dr. Irving Schulman
Professor and Head of the Department of Pediatrics, University of Illinois College of Medicine

Dr. Martin H. Smith
Practicing pediatrician in Gainesville, Georgia, and past Chairman of the Georgia Chapter, American Academy of Pediatrics